

## Case Report

# Focal segmental glomerulosclerosis associated with long-term treatment with zoledronate in a myeloma patient

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## Introduction

Bisphosphonates were designed as synthetic analogues of endogenous pyrophosphate, which act as a regulator of bone metabolism and is found abundantly in bone matrix [1,2]. Non-nitrogen containing first-generation bisphosphonates, such as clodronate or etidronate, which closely resemble pyrophosphate, primarily induce osteoclast apoptosis by intracellular accumulation of non-hydrolyzable ATP analogues [3]. Nitrogen-containing bisphosphonates, such as zoledronate, pamidronate, ibandronate and alendronate, have been found to act on bone-resorbing osteoclasts by inhibiting farnesyl diphosphate (FPP) synthase, a key regulatory enzyme in the mevalonate pathway. Inhibition of FPP synthase prevents post-translational prenylation of small GTPases, causing impaired osteoclast function and sensitizing cells for apoptosis [4–6].

To date, zoledronate is one of the most potent bisphosphonates with very high affinity to bone [7]. It is in widespread use for the treatment of patients with multiple myeloma or bone metastasis due to solid tumours as well as hypercalcaemia of malignancy [8].

Zoledronate has been associated both with dose-dependent and infusion time-dependent acute and chronic renal failure [2,9–15]. Markowitz *et al.* [9] described six patients suffering from underlying multiple myeloma or Paget's disease, who developed zoledronate-associated toxic acute tubular necrosis (ATN). The predominant renal biopsy findings in these patients were marked tubular degenerative

changes. While all biopsies displayed some degree of global glomerular sclerosis, no one exhibited lesions of focal segmental glomerulosclerosis (FSGS) or its morphological variant collapsing glomerulopathy. Both FSGS and its variant collapsing glomerulopathy have been described following treatment with pamidronate [2,16–19] and other drugs, e.g. lithium, interferon- $\alpha$  or heroin [20]. FSGS has also been reported to be associated with viral infections [21], most importantly with HIV [21,22], hepatitis C and parvovirus B19 [23]. Malignant arterial hypertension and hereditary conditions [20] have also been reported to be associated with FSGS. To our knowledge, no patients with collapsing FSGS and nephrotic syndrome associated with zoledronate have so far been described in the literature.

## Case

Sixteen months prior to the current admission, a 65-year-old Caucasian male patient with a history of arterial hypertension, treated with amlodipin 10 mg/day, was evaluated because of lytic vertebral bone fractures. A bone marrow aspirate showed 30% plasma cells and multiple myeloma IgG- $\kappa$  (Durie-Salmon stadium IIIA) was diagnosed. 12 months before the actual hospitalization, the fourth cycle of chemotherapy with vincristine, adriablastin and dexamethasone (VAD) was completed. Ten months before admission, autologous stem cell transplantation was performed after induction chemotherapy with melphalan, because of 50% bone marrow plasma cell infiltration. Another 4 months later, a second autologous stem cell transplantation was done after induction chemotherapy with melphalan, because of persistent bone marrow plasma cell infiltration (5–10%). Two days before admission, a routinely performed bone marrow aspirate showed formal histological remission but remaining atypical plasma cells (<5%).

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A therapy with standard dose zoledronate (4 mg over 15 min) was administered beginning 16 months before the actual hospitalization, for a total of 10 infusions (Figure 1). Because of an elevated plasma creatinine (2.39 mg/dl (211  $\mu$ mol/l)) 2 weeks after the 9th application, the last dose of zoledronic acid was reduced to 3.3 mg.

At admission, the patient presented with elevated plasma creatinine (4.6 mg/dl (410  $\mu$ mol/l)), heavy proteinuria (protein/creatinine ratio 1731 mg/mmol), hypoalbuminaemia (15 g/l), oedema and hypercholesterolaemia (6.6 mmol/l). Acute renal failure with nephrotic syndrome was diagnosed.

Sonography showed normal-sized kidneys without signs of obstruction or mass lesions. Duplex studies of the renal arteries and veins revealed no abnormalities. Serological evaluations for HIV, hepatitis C or hepatitis B virus and parvovirus B19 were negative.

A renal biopsy was investigated by light and electron microscopy as well as immunohistochemistry (Figures 2 and 3). By light microscopy, 12 glomeruli were seen. Two of them were completely obsolescent and five showed perihilar or peripheral segmental sclerosis, with additional hyalinosis and synechia formation in two of them. In one glomerulus, modest protein storage was present in podocytes and in another one there was low-level activation and crowding of the podocytes overlying slightly collapsed loops. Immunohistochemistry showed massive focal and segmental deposits of IgM and complement factors (C1q, C3, C4, C5b-9) in glomeruli with segmental lesions. All other immunoglobulins were absent. Electron microscopy confirmed segmental sclerosis, mild collapse and activation of podocytes and hyalinosis. Complete foot process fusion was present in the

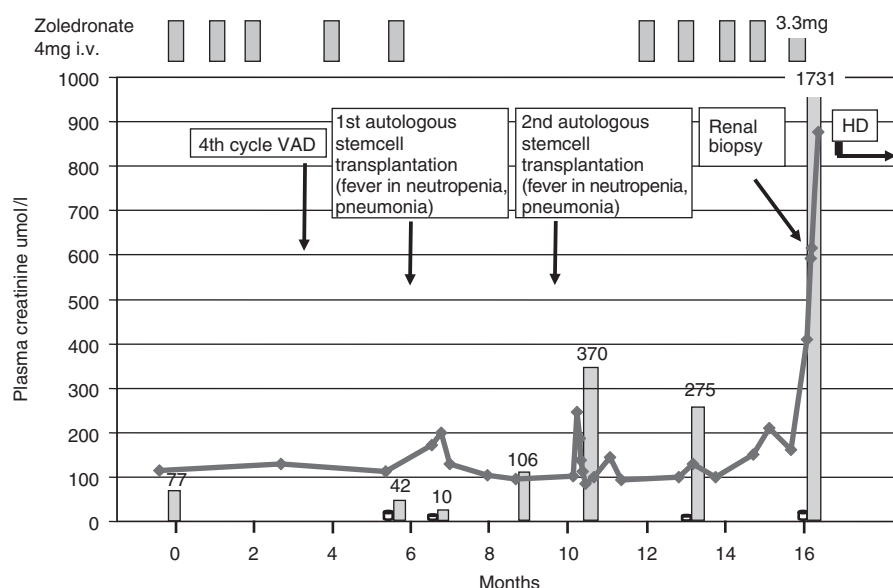
less severely affected glomerular segments. The arterioles showed severe circular hyalinosis and were positive by immunohistochemistry for IgM, complement C3 and C5b-9.

In the tubulo-interstitial space mild diffuse fibrosis, accompanied by scattered infiltration of lymphocytes and histiocytes was present. The tubules showed early signs of atrophy in some areas or luminal dilatation with epithelial cell damage of variable degree: irregular vacuolization, loss of brush border, irregular nuclear distribution and increased mitotic activity (Figure 3). Besides tubular injury, these pathological findings were consistent with FSGS and its collapsing variant. Importantly, there was no evidence of amyloidosis or light chain deposition disease.

Because of rapid decline in renal function, haemodialysis was started 10 days after admission. During the following 10 weeks, no improvement of renal function could be observed.

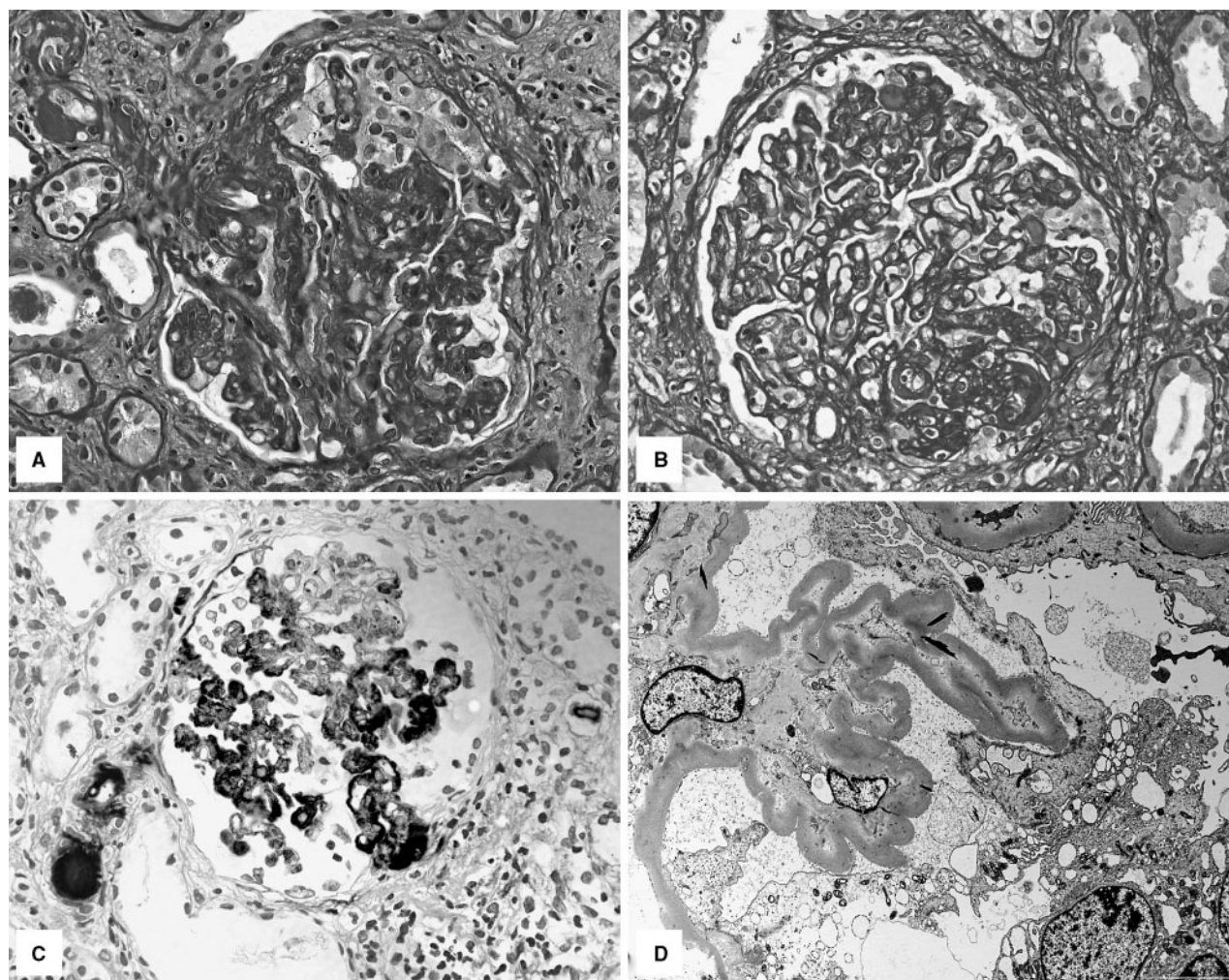
## Discussion

To our knowledge, we report the first patient presenting with collapsing FSGS, nephrotic syndrome and concomitant renal failure associated with the administration of zoledronate. So far, ~80 patients have been described with renal failure associated with the administration of zoledronate [2,9,12–15]. The time from drug initiation to diagnosis of renal failure varied from days [12,15] to 9 months [9,12]. In all available cases, histopathology showed ATN and it was speculated that the pathogenesis may be similar to the effects of bisphosphonates observed in osteoclasts [9].

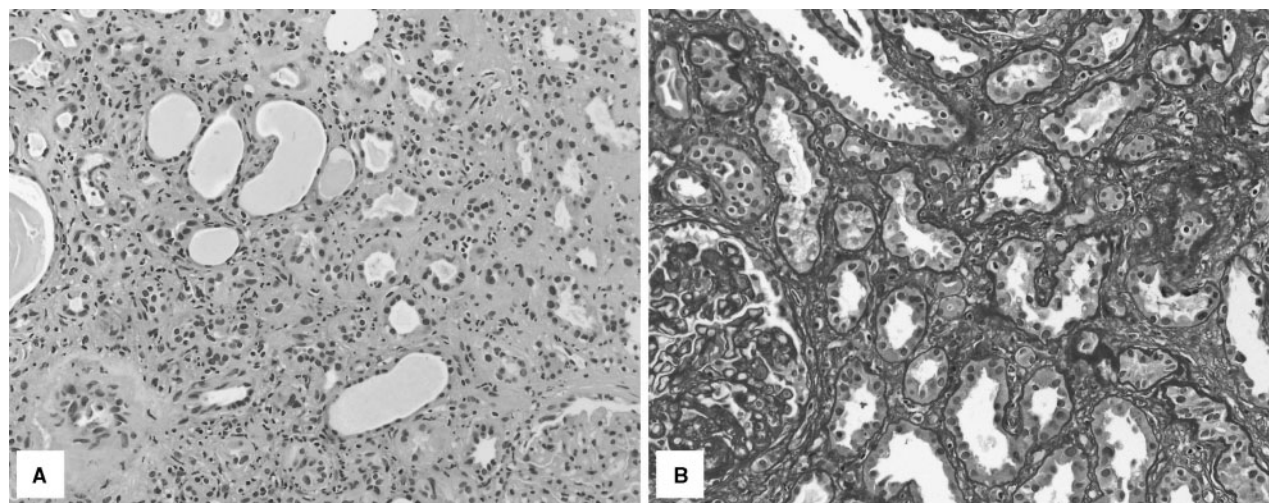


**Fig. 1.** Time course of zoledronate-associated acute renal failure with nephrotic syndrome.  $\blacklozenge$ — $\blacklozenge$  Connected filled diamonds represent plasma creatinine concentration;  $\blacksquare$  Shaded columns represent urine protein/creatinine ratio in mg/mmol (numbers above the columns indicate the ratio) and cylinders represent urine kappa light chain/creatinine ratio  $\square$  (values between 3 and 12 mg/mmol). HD, haemodialysis; VAD, vincristine, adriablastin, dexamethason. To convert creatinine from  $\mu$ mol/l to mg/dl divide by 88.4.





**Fig. 2.** (A) Glomerular segmental sclerosis with slightly collapsed loops and podocyte crowding in Bowman's space. Note medium severe arteriolar hyalinosis of the afferent arteriole (PAS stain, 400 $\times$ ). (B) Segmental sclerosis and hyalinosis with large nodular protein deposits in peripheral loops (red), synechia formation with Bowman's capsule and slight activation of podocytes (trichrome stain, 400 $\times$ ). (C) Lumpy deposits of IgM in peripheral capillary loops, severe staining of peripheral capillaries and nodular deposits in the afferent arteriole (IgM immunohistochemistry in paraffin section, 400 $\times$ ). (D) Completely obsolescent glomerular segment, with denuded basement membranes and activated podocytes in Bowman's space (EM, 2800 $\times$ ).



**Fig. 3.** (A) Tubulo-interstitial space with partly atrophic, partly dilated tubules and scattered interstitial inflammatory cells. Note irregular cell lining in tubules (HE stain, 200 $\times$ ). (B) Interstitial fibrosis and tubules with early signs of atrophy (trichrome stain, 200 $\times$ ).

In our patient, plasma creatinine values rose rapidly 15 months after initiation of zoledronate (Figure 1). The dose of zoledronate was reduced from 4 mg to 3.3 mg for the last infusion after detection of declining renal function. Nevertheless, the patient developed rapid progressive renal failure, finally requiring haemodialysis.

Infection with HIV, hepatitis B or hepatitis C and parvovirus B19 could be excluded. Taking into account the decline of renal function with appearance of nephrotic syndrome within one month and the discussed histopathological features, hypertensive nephropathy was considered an improbable cause for the FSGS. Considering the persistent light chain proteinuria on admission, residual multiple myeloma might explain some of the clinical and histopathological findings. However, lacking evidence of amyloid, IgG- $\kappa$  and electron dense deposits, excluded the diagnosis of amyloidosis or light chain deposition disease. Bisphosphonate-associated nephrotic syndrome with accompanying renal failure portends a poor prognosis. Only about 20% of such patients will experience any degree of recovery and almost half of them need haemodialysis [18].

Currently, all pathological subsets of FSGS are believed to be associated with podocyte dysfunction. Histopathological features include change of normal appearance, plasma vacuolization, hyperplasia and hypertrophy, foot process fusion as well as loss of podocytes [19,20,24,25]. Podocyte dysregulation and cell cycle derangements, leading to de-differentiation and apoptosis, have been implicated in the pathophysiology of FSGS [19,20,25,26]. Pamidronate has been shown to be associated with FSGS [2,16–19]. Barri *et al.* [17] reported five cases of FSGS, including one with collapsing glomerulopathy, associated with the administration of pamidronate. All patients showed variable podocyte injury and extensive foot process effacement.

Similar to zoledronate, ATN has been reported following treatment with pamidronate [2]. Interestingly, the question why pamidronate or zoledronate-associated renal toxicity involves different targets (e.g. tubular cells, podocytes) remains unresolved. It is believed that different dosage regimens and individual susceptibility to renal disease may play a role [17]. Whether inhibition of prenylation of GPTases due to nitrogen-containing bisphosphonates may play a role in podocyte injury is currently unknown, but it is intriguing to speculate that similar mechanisms may be responsible for podocyte as well as osteoclast dysfunction and apoptosis.

In conclusion, we report the first case of zoledronate-associated renal failure with FSGS and nephrotic syndrome. So far, only ATN has been associated in the literature with therapy of zoledronate. Therefore, we believe that it is important to monitor not only creatinine values but also proteinuria for

earlier detection of worsening renal function in patients treated with zoledronate.

*Conflict of interest statement.* None declared.

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